Claims 1, 4, 6-9, 12, 15, 16, 18, 20, 24, 27, 29, 31-34, 36, 38, 47, 48, 51, and 60 have been amended. Claims 11, 17, 40, and 59 have been cancelled, and Claims 61-74 have been added in order to more clearly claim the invention. No new matter is added herewith. Support for the new claims can be found in the specification as filed. Changes to the claims can be seen on a separate page entitled VERSION WITH MARKINGS TO SHOW CHANGES MADE following the signature page. Deletions are in **[bold and brackets]**, and insertions are underlined.

Double Patenting Rejection

The Examiner advised that should claim 58 be found allowable, claim 59 would be objected to under 37 C.F.R. § 1.75 as being a duplicate thereof. Applicants have cancelled Claim 59, thus the rejection is moot.

Rejection Under 35 U.S.C. § 102

Claims 1-3, 5-10, 13-15, 17-21, 27-29, 31, 32, 34, 37, 38, 40, 49-53, and 57-60 were rejected under 35 U.S.C. § 102(b) as being anticipated by Stringer (WO 96/15238).

Stringer discloses recombinant T-lymphocytes produced by transfecting T-lymphocytes with a vector encoding heterologous alpha and beta T-cell receptor polypeptides, which confer specificity of binding of the T-cell to a target cell. However, in contrast to the present invention, the vector encoding the T-cell receptor polypeptide does not deliver a second polynucleotide (for example, a therapeutic gene) to a tumor. The vector in Stringer merely delivers the nucleotide encoding the T-cell receptor polypeptide to the T-cells, which may then be used in adoptive immunotherapy to target cells for immunotherapy mediated by the cytotoxic T-cells themselves. Moreover, Stringer provides no teaching or suggestion that the vector polynucleotide encodes a tumor interacting protein that binds to a trophoblast cell surface antigen. Therefore, Applicants assert that amended Claim 1 is not anticipated by Stringer. Similarly, as claims 27 and claim 31 have also been amended to incorporate the feature that the tumor-interacting protein binds to a trophoblast cell surface antigen, Applicants assert that these claims also cannot be anticipated by Stringer. Further, as claims 2-10, 13-15, 18-21, 28, 29, 32, 34, 37-38, 40, 49-53 and 57-60 are each dependent on one of Claims 1, 27 or 31 and thus require that the tumor-interacting protein

binds to a trophoblast cell surface antigen, these claims are also not anticipated by Stringer. Therefore, Applicants respectfully request withdrawal of the claim rejections on this basis.

Claims 1-9, 15, 16, 20, 24, 27-29, 31, 32, 34, 47, 49-53, 57-60 were rejected under 35 U.S.C. § 102(e) as being anticipated by Wickham (U.S. Patent 5,559,099). Wickham describes adenoviruses comprising a chimeric penton base protein, which includes a non-penton base sequence for targeting an adenovirus to a specific receptor. However, in contrast to the present invention, Wickham neither teaches nor suggests that a vector comprising a polynucleotide encoding a tumor-interacting protein and a second polynucleotide (such as the therapeutic gene) wherein the tumor-interacting protein binds to a trophoblast cell surface antigen could or should be used. Therefore, Applicants respectfully submit that in light of the amendments to Claims 1, 27 and 31, rejections under 35 U.S.C. § 102 should be withdrawn.

Furthermore, it is submitted that new claims 61 to 74 are novel and inventive over the prior art as the vector recited in these claims comprises a polynucleotide encoding the tumor-interacting protein and a second polynucleotide of interest. None of the art of record disclose both of these limitations.

New claims 61 and 63 correspond to previous claims 13 and 14 respectively. The Examiner has alleged that previous claims 13 and 14 are anticipated by Stringer. However, although Stringer discloses that the alpha and beta T-cell receptor polypeptides encoded by the nucleotide delivered by the vector may be provided as a fusion peptide, Stringer does not disclose that the vector may deliver a second polynucleotide (for example, a therapeutic gene) to a tumor. Indeed, the vector in Stringer merely delivers the nucleotide encoding the T-cell receptor to the T-cells. New claims 62 and 64 are dependent on claims 61 and 63 respectively and are based on previous claim 36, to which the Examiner has raised no rejections under 35 U.S.C. § 102.

Independent claim 65 and dependent claim 66 correspond to previous claims 18 and 19 respectively, which the Examiner alleges are anticipated by Stringer. Claim 65 is directed to a retroviral vector comprising a polynucleotide encoding a tumor-interacting protein which recognizes a tumor, wherein the vector delivers a second polynucleotide of interest to the tumor. Although the vectors described in Stringer may be retroviral vectors, Stringer provides no indication that the vector may deliver a second polynucleotide (for example, a therapeutic gene) to a tumor. Claim 66 further requires that the vector comprises a tumor-specific promoter-enhancer. This feature is not disclosed by Stringer.

Independent claim 67 corresponds to previous claim 21 and is directed to a method of delivering a polynucleotide of interest or a product of interest encoded by said polynucleotide of interest to a tumor, comprising delivering the polynucleotide of interest or product of interest to said tumor by use of a vector which delivers the polynucleotide of interest and the product of interest *ex vivo* to the tumor. The Examiner alleges that previous claim 21 is anticipated by Stringer. However, as described above, Stringer merely describes the use of a vector to deliver a nucleotide encoding T-cell receptor polypeptides to T-cells, which can be used in adoptive immunotherapy. In contrast to the methods of the present invention, the vectors in Stringer do not deliver a nucleotide of interest or product of interest to a tumor. Independent claim 68 corresponds to previous claim 25, to which no rejection under 35 U.S.C. § 102 have been raised by the Examiner.

Independent claim 69 is based on previous claim 29, which the Examiner alleges is anticipated by Stringer and Wickham. Claim 69 is directed to a method of treating cancer cells of the haematopoietic cell lineage which comprises administering to cancer cells a gene delivery system comprising a vector comprising a polynucleotide encoding a tumor-interacting protein wherein the tumor-interacting protein recognizes a tumor and wherein the vector delivers a polynucleotide of interest to the cancer cells. As described above, Stringer merely describes the use of a vector to deliver a nucleotide sequence encoding T-cell receptor polypeptides to T-cells, which can be used in adoptive immunotherapy. It does not disclose the use of such vectors to deliver a polynucleotide of interest to cancer cells, nor does it disclose or suggest the use of such vectors to deliver a polynucleotide of interest to cancer cells of the haematopoietic cell lineage.

Independent claim 70 is based on previous claim 38, which the Examiner alleges is anticipated by Stringer. This claim is directed to a method for delivering a polynucleotide sequence to a second cell neighboring a first cell comprising using a vector to deliver the polynucleotide to said first cell, wherein said vector comprises a polynucleotide encoding a tumor-interacting protein which recognizes a tumor and wherein the vector delivers a second polynucleotide of interest to the tumor. This aspect of the present invention is particularly advantageous in that it enables the *in situ* production of a second polynucleotide of interest and or protein of interest from the second polynucleotide of interest in a tumor cell infected by the vector, with subsequent delivery of the polynucleotide of interest and or protein of interest to surrounding cells. Thus according to this aspect of the invention, one need only infect a small

number of cells to achieve a beneficial effect. In contrast, Stringer merely describes the use of a vector to deliver a nucleotide sequence encoding T-cell receptor polypeptides to T-cells, with neither disclosure of use of the vector to deliver a second nucleotide of interest to a tumor cell nor the subsequent delivery of the nucleotide of interest to a neighboring cell.

Independent claims 71 and 72 are based on previous claim 48, which has was not rejected by the Examiner under 35 U.S.C. § 102. Similarly, independent claim 73 corresponds to previous claim 33, to which the Examiner has raised no 35 U.S.C. § 102 rejections. Dependent claim 74 corresponds to previous claim 58 and is dependent on claim 73. As the subject matter of claims 61 to 74 is neither disclosed nor suggested by the cited prior art, it is submitted that these claims are novel and inventive.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 20, 21, 24, 25, 27-29, 33, 34, 38, 49-53, 58, and 59 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art. Applicants submit that the present invention is sufficiently described and exemplified in the specification to enable a person of ordinary skill in the art to carry out the invention. The specification gives extensive guidance on the preparation of vectors of the invention and their uses in methods of gene delivery, which may be used for treatment of diseases such as cancer. For example, the specification gives extensive guidance on vectors which may be used, for example, retroviruses and lentiviruses (pages 13 to 22), suitable modification of the vector to direct expression of e.g. a therapeutic gene and/or the trophoblast cell surface antigen tumor binding protein (for example, see pages 27- 29). Furthermore, the Examples describes specific embodiments of vectors comprising trophoblast cell surface antigen tumor binding proteins (Examples 1, 5, 10-15) and their delivery to macrophages and monocytes (Examples 2 and 6) or to animal models (Examples 4 and 9) with guidance given as to the assessment of efficacy of the macrophage and *in vivo* treatments (e.g. see Examples 3 ,4, 7 , 8 and 9). Example 1 describes the construction of a 5T4 Sab and viral vectors which may be used to express the 5T4 specific Sab in a human cancer cell. Examples 5, 10 and 11 give extensive guidance on the preparation and use of vectors for delivery B7-scFv fusion proteins to 5T4 expressing cells with Examples 12 and 13 describing the construction and use of vectors expressing scFv-IgG and scFv-IgE1 fusions.

Furthermore, Applicants provide herewith the attached declaration of one of the inventors, Dr. Miles Carroll. The declaration contains data which clearly demonstrates:

a) Intra-tumoral delivery of genes which code for scFv proteins specific to 5T4 nucleotide and expression therefrom;

b) Specific expression of a B7-scFv in the sera of Balb c mice;

c) Expression of a B7-scFv in a tumor following intratumoral delivery using the AdB7-scFv vector.

d) The scFv-Hγ1 fusion protein is able to direct cytotoxicity against cells expressing the 5T4 antigen at the cell surface.

e) The genetic delivery of a construct encoding the scFv-Hγ1 fusion protein using the MLV-LscFv Hγ1 to cancer cells leads to secretion of the protein from the cells and their binding back to the cell surface.

Accordingly, it is submitted that claims 20-21, 24-25, 27-29, 33-34, 38-49, 50-53, 58-59 are enabled by the specification as filed. Therefore, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 1, 4, 7, 9, 36, and 47 were rejected under 35 U.S.C. § 112, second paragraph, for being indefinite for reciting the phrase "capable of". This phrase has been deleted from Claims 1, 4, 7, 9, 36, and 47. The Examiner further objects to the terms "recognizes", "delivers", and "interacts" as used in Claims 1, 4, 7, 9, 36, and 47. The term "interacts" has been replaced with the term "binds" in Claim 7. However, Applicants submit that the meaning of the terms "recognizes" and "delivers" in the context of the claims and the present invention would be clearly understood by the skilled person. The term "recognition" is routinely used in biology to refer to the ability of one molecule, for example an antibody, to specifically interact with another molecule, for example an antigen. Similarly, the term "delivers" is routinely used in the context of molecular biology to describe what a "vector" does, i.e. deliver or carry inserted foreign DNA

to a target organism or cell. In addition, Claim 47 has been amended to depend on Claim 6, thus giving the term "protein product of interest" proper antecedent basis. Therefore, Applicants respectfully request withdrawal of the claim rejections on this basis.

Claim 6 was rejected for being indefinite. The Examiner states that it is unclear how the second polynucleotide of interest "expresses" a protein product of interest. Applicants have amended the claim to recite the term "encodes", rather than "expresses" in order to more clearly claim the present invention.

Claim 8 was rejected, because the Examiner asserts that it is unclear what constitutes "a restrictive number of cell types". Applicants have deleted this phrase from the claim in order to more clearly claim the invention.

Claim 14 was rejected for lacking antecedent basis for the phrase "product of interest." However, Claim 14 is dependent on Claim 6 , which provides antecedent basis for this phrase.

Claims 15 and 16 were rejected for reciting the term "functional component". The Examiner states that the specification only defines what preferably constitutes a functional component and thus the term is not clearly defined. Claims 15 and 16 have been amended to include the definition of "functional component" from Claim 17.

Claim 17 was rejected for reciting the term "signaling entity" because the Examiner asserts that the term is not defined in the specification. Claim 17 has been cancelled, thus the rejection is moot.

Claim 18 was rejected for reciting "wherein the vector comprises a retroviral vector." The Examiner states that it is unclear how a vector can comprise a vector. The claim has been amended as suggested by the Examiner to recite "is", rather than "comprises." Applicants respectfully request withdrawal of the 112, second paragraph rejection.

Claim 20 was rejected for reciting "a method of delivering a polynucleotide of interest or a product of interest said polynucleotide of interest to a tumor, comprising..." The Examiner states that the phrase is unclear and further states that the term "product of interest" is undefined. Claim 20 has been amended to specify that the "product of interest" is encoded by "said polynucleotide of interest." In the context of the present invention, the polynucleotide of interest carried by the vector encodes the protein product of interest and thus the "product of interest" will be understood by one of skill in the art to be delivered to the target by the vector.

Claim 24 was rejected for reciting "delivering wherein the polynucleotide of interest or product of interest are delivered..." The Examiner states that it is unclear if both products are delivered together or one or the other is delivered alone. The Examiner further states that the term "product of interest" is undefined. Claim 24 has been amended such that the "product of interest" is defined as a "product of interest encoded by said polynucleotide of interest." Moreover, the term "are" has been amended to recite "is" in order to more clearly claim the invention. Applicants respectfully request withdrawal of the 112, second paragraph rejection.

Claim 27 was rejected as being indefinite. The claim has been amended to state that "said gene delivery system comprises (i) a genetic vector encoding a tumor-interacting protein and (ii) an in vivo gene-delivery system." Applicants respectfully assert that the amended claim more clearly and definitely recites the invention. Thus, Applicants request withdrawal of the 112, second paragraph rejection.

Claim 28 was rejected for the recitation "a method of treating cancer comprising administering the gene delivery system according to claim 27 to the site of a tumor," because the Examiner asserts that the claim could be interpreted in more than one way. Accordingly, Applicants have amended Claim 28 to recite "...the gene delivery system of claim 27." Thus, it is clear that the gene delivery system is not being administered according to a method recited in Claim 27, but rather, that the gene delivery system of claim 27 is being administered. Applicants respectfully request withdrawal of the 112, second paragraph rejection.

Claim 29 was rejected for reciting the phrase " the method of claim 28 wherein the tumor is of haematopoietic cell lineage," because it is unclear what the site of a tumor would be when the tumor is of haematopoietic lineage. Claim 29 has been amended to recite "a method of treating cancer of cells of the haemoatopoietic cell lineage comprising administering the gene delivery system according to claim 27 to cancer cells." Applicants assert that amended Claim 29 clearly recites a method according to the present invention as it relates to haematopoietic cells.

Claim 32 was rejected for reciting the phrase "effector domain" because the Examiner states that it is unclear what constitutes an "effector domain." Claim 32 has been amended to state that a tumor-interacting protein comprises one or more effector domains selected from the group consisting of an enzyme, a pro-drug activating enzyme, a toxin, all or part of a cytokine, an effector domain of an immunoglobulin heavy chain, a domain which activates macrophage FcgR

I, II, or III receptors and a domain which confers protein stability ex vivo and or in vivo. Basis for such examples of "effector domains" can be found in the specification on pages 31-33.

Claim 33 was rejected as being unclear for reciting "one or more tumor-interacting protein genes." All claims depending on Claim 33 were also rejected for this reason. Claim 34 was rejected as being unclear for the recitation "a combination of a cytokine or a cytokine-encoding gene and one or more tumor-interacting protein encoding genes." Claims 33 and 34 have been amended according to the Examiner's suggestions to more clearly claim the invention. In response to the Examiner's concern regarding the phrase "the site of the tumor", it is believed that this term would be clearly understood by one of ordinary skill in the art, based on common general knowledge in the field and the context of the term in the claims and specification of the present application. Nonetheless, Applicants have amended Claim 34 to recite "a method of delivering a gene to a tumor, comprising delivering genes encoding tumor-interacting proteins directly to the tumor, wherein said genes are delivered using a vector according to claim 1." Thus, Applicants respectfully request the Examiner to withdraw the 112 rejection.

Claim 38 was rejected as being indefinite for reciting the phrase "in close association with the second cell." Claim 38 has been amended to refer to a method for delivering a polynucleotide sequence to a second cell comprising using a vector according to claim 1 to deliver the polynucleotide to a first cell neighboring said second cell. Basis for this amendment can be found in claim 38 as originally filed and in the specification, page 25 lines 17 to 19, page 43 lines 25-27, and page 44 lines 1-2. It is believed that this amendment clearly defines the subject matter of the claim. The term "neighboring cell" is routinely used in the field of gene therapy to refer to cells in close proximity to a transduced cell, which may benefit from the bystander effect. As such, in the context of the specification, Applicants assert that the claim is clear.

Claim 40 was rejected for reciting the phrase "A process for preparing a tumor-binding protein comprising expressing a polynucleotide encoding a tumor-binding protein in a vector according to claim 1." Claim 40 has been cancelled, and thus the rejection is moot.

Claims 49 and 50 were rejected for being indefinite for reciting "the method...wherein the vector is used to deliver the polynucleotide of interest and or product of interest *in vivo* to the tumor." As stated above, in regard to Claim 20, by delivering a polynucleotide of interest encoding a product of interest to a cell, the "product of interest" is delivered. By virtue of

amendments to Claims 20 and 24, the protein of interest has been defined in Claims 49 and 50 as being encoded by said polynucleotide of interest.

Claim 51 was rejected for being indefinite for reciting the phrase "wherein the tumor-interacting protein is a TBP" because "TBP" is not defined in the claim. "TBP" has been replaced by the term "tumor-binding protein."

Claim 52 was rejected for being indefinite for reciting the phrase "the method of claim 28 wherein the gene delivery system is administered systemically." Applicants submit that the phrase "administered systemically" is not indefinite. The skilled person is aware that systemic administration refers to any method of administration in which a compound is distributed to a site of action by delivery via the cardiovascular circulation in contrast to direct administration to the site of action. Moreover, the specification refers to delivery either by direct injection or by systemic delivery (for example, see page 35 lines 10-12). Examples of systemic routes of administration are also given on page 35 line 27 to page 36 line 14. Thus, Applicants respectfully request the Examiner to reconsider and withdraw this rejection under 112, second paragraph.

Claim 60 was rejected for reciting the limitation "protein product of interest" because it lacks sufficient antecedent basis. The claim has been amended to be dependent on Claim 6 which provides antecedent basis for the "protein product of interest."

In light of the forgoing remarks and amendments, Applicants asset that the claims clearly recite the present invention. Applicants respectfully request withdrawal of the claim rejections under 35 U.S.C. § 112, second paragraph.

Conclusion

Should any issues arise which may delay prosecution of the present application, the Examiner is respectfully invited to contact the under-signed attorney at the telephone number below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

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Filed : March 21, 2000

Dated: 4-24-02 By: [signature]

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Deletions are in **[bold and brackets]**, and insertions are underlined

IN THE CLAIMS:

Please cancel Claims 11, 17, 40 and 59.

Please amend the following claims:

1. **(TWICE AMENDED)** A vector comprising a polynucleotide encoding a tumor-interacting protein wherein the tumor-interacting protein **[is capable of recognizing a tumor]**binds to a trophoblast cell surface antigen and wherein the vector **[is capable of delivering]**delivers a second polynucleotide of interest to the tumor.

4. **(TWICE AMENDED)** The vector according to claim 1 wherein the vector **[is capable of delivering]**delivers the second polynucleotide of interest to the interior of a tumor mass.

6. **(TWICE AMENDED)** The vector according to claim 1 wherein the second polynucleotide of interest **[expresses]**encodes a protein product of interest.

7. **(TWICE AMENDED)** The vector according to claim 1 wherein the polynucleotide comprises at least one tumor binding domain **[capable of interacting with]**which binds with at least one tumor-associated cell surface molecule.

8. **(TWICE AMENDED)** The vector according to claim 7 wherein the tumor-associated cell surface molecule is selectively expressed on one cell type **[or on a restrictive number of cell types]**.

9. **(TWICE AMENDED)** The vector according to claim 1 wherein the vector **[is capable of delivering]**delivers the second polynucleotide of interest to a selective tumor site.

12. **(TWICE AMENDED)** A vector according to claim **[11]**1 wherein the **[tropoblast]**trophoblast cell surface antigen is the 5T4 antigen.

15. **(TWICE AMENDED)** The vector according to claim 1 wherein any nucleotide sequence selected from the group consisting of: the polynucleotide encoding the tumor-interacting protein, the second nucleotide sequence of interest, and both further comprises a polynucleotide sequence which encodes at least one additional functional component, wherein the additional functional component is selected from the group consisting of a signal peptide, an immune enhancer, a toxin and a biologically active enzyme.

16. **(TWICE AMENDED)** The vector according to claim 6 wherein any protein selected from the group consisting of the tumor-interacting protein, the product of interest, and both, further comprises at least one additional functional component, wherein the additional functional component is selected from the group consisting of a signal peptide, an immune enhancer, a toxin and a biologically active enzyme.

18. **(TWICE AMENDED)** The vector according to claim 1 wherein the vector **[comprises]**is a retroviral vector.

20. **(TWICE AMENDED)** A method of delivering a polynucleotide sequence of interest or a product of interest **[said polynucleotide of interest]**encoded by said polynucleotide of interest to a tumor, comprising delivering the polynucleotide of interest or product of interest to said tumor by use of the vector of claim 1.

24. **(TWICE AMENDED)** A method of treating cancer in a mammal, the method comprising delivering a polynucleotide of interest or a product of interest encoded by said polynucleotide of interest to a tumor, wherein the polynucleotide of interest or product of interest **[are]**is delivered to the tumor by use of the vector according to claim 1.

27. **(TWICE AMENDED)** A gene delivery system for targeting one or more genes encoding a tumor-interacting protein to a tumor, **[comprising]**wherein said gene delivery system comprises (i) a genetic vector encoding a tumor-interacting protein and (ii) an *in vivo* gene-delivery system, wherein said tumor interacting protein binds to a trophoblast cell surface antigen.

28. **(TWICE AMENDED)** A method of treating cancer comprising administering the gene delivery system **[according to]**of claim 27 to the site of a tumor.

29. **(TWICE AMENDED)** A method of **[claim 28 wherein the tumor is]**treating cancer of cells of the haematopoietic cell lineage comprising administering the gene delivery system according to claim 27 to cancer cells.

31. **(TWICE AMENDED)** A genetic vector comprising a polynucleotide encoding a tumor-interacting protein, operably linked to an expression regulatory element selectively functional in a cell type present within a tumor mass, wherein said tumor interacting protein binds to a trophoblast cell surface antigen.

32. **(TWICE AMENDED)** The genetic vector of claim 31 wherein said tumor-interacting protein additionally **[comprising]**comprises one or more effector domains selected

from the group consisting of an enzyme, a pro-drug activating enzyme, a toxin, all or part of a cytokine, an effector domain of an immoglobulin heavy claim, a domain which activates macrophage FcgR I, II or III receptors and a domain which confers protein stability *ex vivo* and/or *in vivo*.

33. **(TWICE AMENDED)** A method of treating cancer in a mammal which comprises administering a combination of a cytokine or a cytokine-encoding gene and one or more **[tumor-interacting]** genes encoding a tumor-interacting protein, wherein said tumor-interacting protein binds to a trophoblast cell surface antigen.

34. **(TWICE AMENDED)** A method of delivering a gene to **[the site of]** a tumor comprising: delivering genes encoding tumor-interacting proteins **[encoding genes to the site of a tumor]**directly to the tumor, wherein said genes are delivered using a vector according to claim 1.

36. **(TWICE AMENDED)** The vector of claim 14 wherein the fusion protein is **[capable of being]** secreted.

38. **(TWICE AMENDED)** A method for delivering a polynucleotide sequence to a second cell comprising **[placing a first cell containing the vector of claim 1 in close association with the second cell]**using a vector according to claim 1 to deliver the polynucleotide to a first cell neighboring said second cell.

47. **(ONCE AMENDED)** The vector according to claim **[1]**6 wherein the vector **[is capable of delivering]**delivers the **[protein]** product of interest to the interior of a tumor mass.

48. **(ONCE AMENDED)** The vector of claim **[17]**15 wherein the **[signaling entity]**additional functional component is a signal peptide.

51. **(ONCE AMENDED)** The gene delivery system of claim 27 wherein the tumor-interacting protein is a **[TBP]**tumor binding protein.

60. **(ONCE AMENDED)** The vector of claim **[40]**6 wherein the protein product of interest is therapeutic.